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Editorial Comment

Predicting Outcome After Implantable Cardioverter-Defibrillator Therapy

A New Piece to the Puzzle?*

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In this issue of the *Journal*, Tereshchenko et al. (1) examine local injury current (LIC) measured from a recording of the right ventricular electrogram after an implantable cardioverter-defibrillator (ICD) shock during ICD implantation as a predictor of heart failure progression. The importance of this study is highlighted by a series of observations made from large randomized clinical trials of ICD therapy performed over the last decade (2–4). Patients with reduced left ventricular function who receive appropriate or inappropriate ICD shocks have been shown to have a worse short- and long-term prognosis from myocardial dysfunction and heart failure. In the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial-II) study, patients who received an appropriate ICD shock had a 3-fold increase in later mortality over those who did not receive an appropriate shock and a 2-fold increase in

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mortality if they received and inappropriate shock. In the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) study, an appropriate shock was associated with a 5-fold increase in later mortality and an inappropriate shock with a 2-fold increase in mortality. What still remains poorly understood is whether the shock(s) induce myocardial trauma and dysfunction that increase mortality, or whether the ventricular arrhythmias and shocks are a marker of patients at increased risk.

Isolated reports of acute myocardial stunning manifesting as pulseless electrical activity after ICD testing have served as a concern for decades (5,6), and the recent publications of increased mortality after ICD shocks have focused interest on the possible mechanism(s). Mitchell et al. (5) analyzed the mechanisms of sudden death in patients with ICDs. In this retrospective analysis of 317 patients, they attributed 29% of the deaths to post-shock electromechanical dissociation, which they described as "cardiac annihilation" and attributed this to ischemia in some cases.

A large number of animal studies highlight a spectrum of changes after electrical shocks. These changes include alterations in electrophysiologic function, hemodynamic function, biochemical alterations, and cellular morphology. The shock strength that causes dysfunction in the normal heart may be markedly different from that causing dysfunction in the heart with pre-existing cardiac dysfunction. Tokano et al. (7) demonstrated that ICD shocks in humans of >9 J delivered either during sinus rhythm or during ventricular fibrillation (VF) were associated with a 10% to 15% reduction in the cardiac index, which persisted for up to 4 min. Shocks of lesser energy did not depress the cardiac index. The amount of dysfunction increased with increasing shock strength, and they proposed that shock strength and not VF was responsible for transient worsening of myocardial function. Yamaguchi et al. (8) studied shocks in conventionally perfused and underperfused rat hearts during both sinus rhythm and VF. In the ischemic underperfused hearts, there was significant worsening in heart function after shocks given during either sinus rhythm or VF, and the dysfunction was proportional to the shock strength. In the normally perfused rat heart, there was no impairment after shocks whether given during sinus rhythm or VF. In a resuscitation model, Xie et al. (9) put rats into VF for 4 min followed by mechanical ventilation and pre-cordial compressions for 6 min before defibrillation. They found proportionally higher shock strengths were associated with more myocardial depression and worsening mortality. In an isolated perfused rat heart with VF, Zaugg et al. (10) showed the mechanism of myocardial dysfunction is caused by reduced myofilament calcium responsiveness due to myocyte calcium overload,

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similar to the mechanism of myocardial damage in atrial myocytes after prolonged atrial fibrillation.

From these animal studies, it is clear that shocks may acutely worsen heart failure and exacerbate ventricular dysfunction. Myocardial dysfunction is proportional to the amount of prior myocardial damage and the shock strength. In 1986, Eysmann et al. (11) showed that in patients with severe ischemic heart disease who underwent electrophysiology studies and had inducible VF or unstable ventricular tachycardia (VT) requiring defibrillation, up to 60% of patients had ST-segment changes after rescue defibrillation. This was in contrast to the rare ST-segment changes they saw in patient with structurally normal hearts when cardioversion from supraventricular tachycardia or atrial fibrillation was performed (11). Electrocardiographic changes were seen both with internal and external cardioversion. Isolated clinical reports suggest that left ventricular systolic function may take weeks to normalize after cardiac arrest (12). Finally, biochemical markers of myocardial damage, such as a rise in troponin levels, have been seen after ICD implantation, but the elevation in troponin is generally small (13).

It is against the backdrop of these studies that the results from the present study must be put into perspective. Tereshchenko et al. (1) performed a prospective observational study to identify an early marker of functional impairment after an ICD shock delivered during defibrillation threshold testing as part of ICD implantation and as a predictor of future clinical events. They hypothesized that a transient injury current on the local bipolar right ventricular electrogram after an induced VF rescue shock might identify patients at increased risk for death and heart failure. In this prospective study, they enrolled 310 patients with either a primary or secondary indication for an ICD who had New York Heart Association functional class I to III heart failure. Fifteen percent of the patients had prior ICD systems and underwent generator change without implantation of a new lead. All patients had Medtronic (Minneapolis, Minnesota) dedicated true bipolar leads. VF was induced with T-wave shocks, and, after appropriate termination by the device, the near field right ventricular bipolar electrograms was examined for LIC. Data were collected only for first and not repeat shocks. Significant LIC occurred in 106 (34%) patients. Patients with ventricular paced beats or distorted beats were excluded. The LIC measurement was reproducible and consistent.

The combined end point was death or congestive heart failure (CHF) exacerbation with hospitalization. During follow-up of 29.3 ± 15.0 months, this occurred in 40 patients (12.9%). The majority of events were CHF exacerbations. Appropriate ICD shocks were seen in 78 patients (25.2%). CHF was twice as likely in patients receiving shocks (20.5% vs. 10.3%; $p = 0.02$). The major finding of this study is that in patients with new ICD leads with LIC, subsequent VT/VF episodes with appropriate ICD shocks predicted CHF progression. There was only a 40% event-free survival in LIC patients with shocks versus 80% in LIC patient without shocks ($p = 0.006$). In patients who were LIC negative, the event-free survival was good whether they had shocks or not (87% event free vs. 88%, $p = 0.683$). Thus, only patients with LIC had a markedly worse prognosis after appropriate ICD therapy. LIC was less frequent and not predictive in patients with chronic leads undergoing generator change, although clearly not enough patients were studied in this group to make definitive conclusions.

The authors propose that "3 hits" are required to explain the genesis of LIC. These factors are an underlying condition that leads to worsening CHF, mechanical injury from acute lead placement, and the ICD shock. They speculate that the LIC may be caused by electroporation. Electroporation is permeabilization of the cell membrane caused by high transmembrane potentials from a shock or electric field (13,14). This disrupts the cardiac tissue equilibrium at the cellular level allowing alterations in transmembrane ion concentration gradients, which can lead to ST-segment changes, arrhythmias, and depressed myocardial function. Other mechanisms for the genesis of LIC might be considered by careful study of ion currents in animal models of defibrillation threshold testing. Electroporation may be one of the causes of acute decompensation of heart function after defibrillation, and may be more likely found in patients prone to future heart failure exacerbations (15). Patients that are prone to electroporation may also be prone to suffering more myocardial injury from a shock, so it is unclear if LIC after shock is just a marker of a sicker heart or if these are patients that shocking makes worse. Future studies may delineate this.

If the results were demonstrated in patients with chronic ICD leads, then ST-segment changes could be measured by ICDs after all shocks as a marker and possibly trigger an alarm for physicians. The measurement could trigger an alert on a remote monitoring device and identify patients who need particularly careful management of their underlying heart disease and heart failure. One must wonder, whether by identification of LIC and early risk stratification leading to more aggressive medical management whether we could also alter or effect patient outcomes. Future studies might also examine whether LIC is predictive of short- and long-term outcomes in patients who undergo upper limits of vulnerability testing in place of defibrillation threshold testing. It is also unknown whether this or a similar measurement can be obtained in patients who receive integrated bipolar ICD leads. The relevance of measurements of LIC under other circumstances is unknown, for example, after an inappropriate shock or after a second or third episode of induced VT or VF. The reproducibility of this measurement in the short and long term will need study as well. Also, is this measurement changed by revascularization, medical therapy for heart failure, or medical therapy for ischemic heart disease?

This is an important and well done study that is the first to demonstrate a clear and simple intracardiac marker for patients who do poorly after appropriate ICD shocks. These patients may benefit from increased follow-up and aggressive medical therapy. Only future prospective studies can answer some of these questions and should be on the mind of clinicians who are trying to improve the prognosis of patients who receive ICD shocks.

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